immunodeficiency virus operatively linked to DNA which is a promoter region, in a physiologically acceptable carrier, wherein the DNA transcription unit is expressed in cells of the vertebrate, [and] thereby eliciting a humoral immune response, a [or] cell-mediated immune response, or both, against the [desired] antigen, whereby the [vertebrate] mammal is protected from disease caused by the immunodeficiency virus.

C4 Cont

52. (Amended) A method of immunizing a [mammal] vertebrate against an influenza, said method comprising administering to the [mammal] vertebrate a DNA transcription unit comprising DNA encoding an antigen of the influenza virus operatively linked to DNA which is a promoter region, in a physiologically acceptable carrier, wherein the DNA transcription unit is expressed in cells of the vertebrate, [and] thereby eliciting a humoral immune response, a [or] cell-mediated immune response, or both, against the [desired] antigen, whereby the vertebrate is protected from disease caused by the influenza virus.

Cancel D5

C5

53. (Amended) The method of Claim 52, wherein the DNA transcription unit is administered in combination with at least one [or more] additional DNA transcription [units, each] unit comprising DNA encoding a different antigen of an influenza virus operatively linked to a promoter region.

Remarks

Applicants note that claims 8, 27 and 39 were cancelled in a Preliminary Amendment filed in the U.S. Patent and Trademark Office on June 19, 1995. Claims 1,

16, 17, 32, 44, 52 and 53 have been amended for clarity and consistency, and to define the invention more accurately.

Claims 1-7, 9-26, 28-38, and 40-56 are pending.

Objection to the Drawings

Applicants acknowledge the objection to the drawings. Formal figures addressing this objection will be filed at a later date.

Objection to the Disclosure

The informality identified by the Examiner has been corrected.

Objection to the Specification under 35 U.S.C. 112, first paragraph

The Examiner objected to the specification as failing to provide an enabling disclosure. The Examiner stated that:

> There is... a lack of guidance given regarding the composition, dosage and administration regimens that humans would require for protection for the following reasons: 1) The data cited by the applicant also lends itself to a high degree of unpredictability. 2) Table 2 illustrates the unpredictability in the type of response achieved by the influenza vaccine. Because of the variability of these results it would be difficult for one skilled in the art to determine the appropriate variables suitable for use in humans (route of administration, dosages, promoters, boosters, etc.). 3) Due to the recognized unpredictability in the duration of expression, DNA stability and the complexity of the immune system in the diverse types of animals encompassed by the claims, undue experimentation would be required to practice the claimed invention.

Applicants respectfully disagree with this assessment. While the results depicted in Table II demonstrated some variability in the degree of protection, as shown by a rate

of protection ranging from 28% to 83% of vaccinated birds, the overall results of the experiment indicated that highly significant protection against mortality was achieved in the experiments: 28 out of 56 vaccinated birds survived, whereas only one of 55 control birds survived (see the Specification at page 17, line 30, through page 18, line 4). Furthermore, Applicants respectfully submit that the animal models for influenza described in the Specification are appropriate models for prediction of results in other animals. The animal models cited in the Specification are frequently used as experimental models for influenza, and therefore can be considered to be reasonably predictive of successful immunization against influenza in other animals, including humans. For example, ferrets are a recognized host for experimental influenza virus infections, because they are permissive hosts for human influenza viruses (see Fields, ed., Virology, 2nd Edition (1990), Volume I, pp. 1114-1115; copies of these pages are attached as Exhibit 1). Applicants further submit that the animal and disease models described in the Specification are representative of those animals which can be treated by the methods of the current invention, and those diseases for which vaccines can be used in the methods of the current invention.

The Examiner also stated that "the extrapolation of animal studies in general as they relate to gene transfer in humans should be done with caution", citing Ledley, Haynes, Hoffenbach *et al.*, and Butini *et al.* The Examiner cited a portion of the Ledley reference which is directed to gene transfer using retroviral vectors. Ledley stated that:

> While animal experiments are useful for assessing specific aspects of gene transfer, there is no data explicitly supporting the contention that animal experiments can presage the outcome, efficacy, or safety of human applications. The details of anatomy, cell biology, genetics, and immunology of other

> species do not duplicate the vicissitudes of human biology, *particularly when considering retroviral vectors whose infectivity, tropism, and pathology is naturally species specific....*(emphasis added).

Applicants respectfully submit that the Ledley reference is not pertinent to the current invention.

The Ledley reference discusses clinical considerations in the design of protocols for somatic gene therapy. The gene therapy contemplated in the Ledley reference is somatic gene therapy, in which a gene is transferred into somatic cells for the purpose of curing genetic defects. Gene transfer, as described in the Ledley reference, involves the transfer and expression of a gene in an individual, when the transfer and expression of the gene is for scientific research, rather than for therapeutic purposes (see page 79, top of left column). Study of gene transfer precedes gene therapy.

The teachings of the Ledley reference differ from the current invention in two critical aspects: first, the Ledley reference pertains to gene therapy for the cure of genetic conditions, and the current invention pertains to immunization for prevention of disease caused by an infectious agent (i.e., non-genetic disease). Second, the Ledley reference discusses retroviral vectors (which are self-replicating) and difficulties associated with them, and the current invention utilizes DNA constructs which are not self-replicating. The DNA constructs circumvent the species-specific problems of infectivity, tropism, pathology, as the DNA is expressed directly by the cellular machinery. Therefore, the warnings expressed in the Ledley reference regarding the propriety of extending animal studies to humans are not relevant to the methods of the current invention: the use of the DNA constructs of the invention is entirely different from, and contemplates

different goals than, the gene transfer and therapy described in the Ledley reference.

The Examiner also cited a discussion of animal models in the Haynes reference (Science 260:1279 (1993)), which states that:

> *Animal models.* In spite of an extraordinary amount of work in search of an animal model for human AIDS, no animal model exactly mirrors human HIV infection. In general, current animal models of HIV or simian immunodeficiency virus (SIV) infection either do not develop AIDS symptoms, do not develop immune responses analogous to human anti-HIV T and B cell responses, or involve the use of endangered species such as chimpanzees. Thus, many important scientific questions of HIV vaccine development must be answered in human clinical trials.
>
> *Correlates of protective immunity against HIV.* Because of a lack of an animal model of human AIDS and because a cohort of individuals naturally resistant to HIV infection is not available, the immune correlates of protection against HIV are not known. For those working on a preventive HIV vaccine, lack of these critical data has forced the design of experimental immunogens that induce some or all of the types of immune responses that are surmised, but not yet known, to be protective against HIV (Table I). (citations omitted)

It appears that the Examiner's concern relates to a purported lack of an appropriate animal model for HIV infection. However, Appropriate models do exist. The model described in the Specification in Example 14 (at page 55, line 29, through page 57, line 8), which uses Rhesus macaques, is an appropriate predictive model for immunodeficiency virus infection and immunization in humans, as described by Almond *et al.* (*Lancet 345*:1342-1344 (1995); Exhibit 2).

It is also noteworthy that the Haynes reference, cited by the Examiner, does not mention DNA constructs as a type of experimental immunogen for HIV vaccine development

(Table 2). Although the Haynes reference does indicate that "direct immunization with complementary DNAs of HIV proteins" has been contemplated for HIV vaccine development, such DNAs are, in fact, a teaching away from the current invention. Complementary DNAs are designed to inactivate HIV DNA, by binding of the complementary DNAs to HIV DNA. In contrast, the DNA constructs of the current invention are designed to be expressed in the individual, and thereby generate an immune response. Thus, the Haynes teachings are not applicable to the current invention.

The Examiner follows the citation from the Haynes reference with a discussion of generating protective CTL response against HIV. The Examiner cites Hoffenbach *et al.* (*J. Immunol. 142(2)*:452-462 (1989)), stating that:

> The art has shown that structural, enzymatic and regulatory proteins from HIV-1 can serve as CTL targets. But, as concluded by Hoffenbach *et al.* on page 459, 'no clear correlation exists at present between the presence of HIV-specific CTL and resistance to progression toward AIDS.' (citation omitted). Therefore, it is clear that despite an initial strong CTL response to HIV, patients will eventually develop AIDS. Consequently, it is unpredictable as to whether stimulation of an HIV-specific antibody or HIV-specific CTL response by applicant's methods would result in a beneficial, protective immune response to prevent HIV infection.

The Examiner then finds further support for these statements in the Butini *et al.* reference. The Examiner discusses the comparison of CTL activity in two patients with HIV infection in the Butini *et al.* reference, and states that "Evidently, the presence of high levels of circulating HIV-specific CTLs cannot [be] directly extrapolated to inhibition of viral spread."

Given the Hoffenbach *et al.* and Butini *et al.* references, the Examiner concluded that:

[A]pplicant's methods and compositions as claimed are not supported by evidence that is demonstrative or predictive of immunoprotection against... HIV or SIV.

Applicants respectfully disagree with this assessment.

The Examiner's concern appears to be related to the lack of correlation between CTL activity and protection against disease. The Hoffenbach *et al.* and the Butini *et al.* references cited by the Examiner describe investigation of HIV-specific CTL activity in humans infected with the HIV virus. The Hoffenbach *et al.* reference describes high frequency of HIV-specific cytotoxic T lymphocytes (CTL). The quantities of CTL and CTL precursors decreased over time as the clinical and immunological status of the infected individuals deteriorated. The Butini *et al.* reference describes high CTL activity in a patient with rapidly progressive disease; no CTL activity in a patient with no progression of disease; and moderate CTL activity in a patient with slowly progressive disease.

The data described in the references cited by the Examiner differ in their conclusions regarding the relationship between CTL response to an antigen and protection against disease. In view of the small samples used in the Hoffenbach *et al.* and Butini *et al.* references, however, Applicants question whether any conclusions can be drawn concerning the relationship between CTL response to HIV and progression of disease. Furthermore, Applicants have not claimed a specific CTL response; rather, the claims are drawn to protection against disease. Applicants have conducted experiments to investigate protection against disease in an appropriate animal model. As described in the Declaration of Dr. Harriet Robinson Under Rule 1.132, Applicants have conducted a trial assessing the effects of DNA vaccination in a model of simian immunodeficiency virus. Briefly, an experimental vaccine

consisting of five DNA plasmids expressing different combinations and forms of simian immunodeficiency virus-macaque (SIVmac) proteins was evaluated for the ability to protect against a highly pathogenic uncloned SIVmac251 challenge. The uncloned SIVmac251 challenge virus is a 'difficult to neutralize' stock that causes $\geq$ 50% incidence of AIDS during the first year of infection. The trial protocol was similar to that set forth in the Specification in Example 14, at pages 55-57. The DNA plasmids used in the trial were similar to those described in the Specification in Example 13, at pages 53-55. Rhesus macaques were inoculated with DNA at 1 and 3, 11 and 13, and 21 and 23 weeks. Four macaques were inoculated intravenously, intramuscularly and by gene gun inoculations ("multiple route" animals). Three received only gene gun inoculations, and two control monkeys were inoculated with control plasmids by all three routes of inoculation.

Neutralizing antibody titers were present in all vaccinated monkeys after the second cluster of inoculations; these titers were transient, and were not boosted by the third cluster of inoculations. Cytotoxic T-cell activity for *Env* was also raised in all of the vaccinated animals. The temporal appearance of cytotoxic T-cells was similar to that of antibody. While antibody responses fell with time, cytotoxic T-cell responses persisted. The SIVmac251 challenge was administered intravenously two weeks following the last immunization. The DNA immunizations did not prevent infection or protect against CD4+ cell loss, and long term chronic levels of infection were similar in the vaccinated and control animals. However, viral loads were reduced to the chronic level over a shorter period of time in the vaccinated animals (six weeks), than in the control animals (12 weeks). At the time the trial was terminated (one year post-challenge), the three monkeys vaccinated solely with

the gene gun, as well as one of the control monkeys, succumbed to opportunistic infection. However, the four "multiple route" monkeys did not demonstrate any clinical signs of disease (AIDS) during the course of the trial.

The Examiner further concluded that:

> [A]pplicant's methods and compositions are not indicative of protection against influenza in animals other than chickens, mice and ferrets.

Applicants respectfully disagree with this assessment. As discussed above, the animal models described in the Specification are representative of those animals which can be treated by the methods of the current invention, and are appropriate predictive models for protection against disease in other animals. Furthermore, the diseases investigated are representative of diseases for which vaccines can be used in the methods of the current invention.

In summary, the Examiner stated that:

> Since applicant's have not demonstrated a consistent and reproducible stimulation of antibody formation, or CTL activity against certain antigens, the skilled artisan would not accept these responses as correlative of a protective immune response against the corresponding pathogen for the scope of the invention as claimed.

Applicants respectfully disagree with this assessment. It is not necessary to demonstrate stimulation of antibody formation, or CTL activity, in order to have a protective effect. Stimulation of antibody formation is indicative of immune response to an antigen, but is not necessary for protection upon challenge. For example, in the Specification at page 30, line 24, and subsequent pages (Example 7), DNA vaccinations and booster inoculations raised only low to undetectable titers of antibody; however, protection occurred in animals that did not have

detectable levels of anti-influenza antibodies before challenge. Furthermore, cytotoxic T lymphocyte response to an antigen is not necessarily indicative of protection. For example, cytotoxic T lymphocytes are not a necessary component for protective immunizations against influenza virus in the murine model (see Scherle, P.A. *et al.*, *J. Immunol. 148*:212-217 (1992); Eichelberger, M. *et al.*, *J. Exp. Med. 174*:875 (1991); copies of these references are attached as Exhibits 3 and 4). In contrast, in the chicken influenza virus model, cytotoxic T lymphocyte responses are not associated with protection (Brown, D. W. *et al.*, *AvianDiseases 36*:515-520 (1992); a copy of this reference is attached as Exhibit 5). Thus, it is known in the art that production of cytotoxic T cells does not necessarily correlate with protection upon challenge.

Rejection of Claims under 35 U.S.C. 112, first paragraph

The Examiner rejected Claims 1-56 for the reasons set forth in the objection to the Specification. In view of the arguments presented above, Applicants respectfully submit that this rejection is obviated.

The Examiner further stated that:

> Specifically, claims 45-49 and 53-56 are not enabled in the specification. Nowhere in the specification does the applicant discuss or provide examples of immunizing with multiple DNA transcription units encoding proteins from the influenza virus. Although one example of immunizating [sic] with multiple transcription units in the case of HIV is given, it [is] not apparent to the examiner that this example is representative of all the possible permutations that are encompassed by the claims.

Applicants respectfully disagree with this assessment. Applicants note that Claims 45-49 are dependent, either directly or indirectly, on Claim 44. Claim 44 describes a method of immunizing a mammal against an immunodeficiency

virus, by administering a DNA transcription unit comprising DNA encoding an antigen of the immunodeficiency virus operatively linked to DNA which is a promoter region. Claims 45-49 are drawn to methods of Claim 44, in which the DNA transcription unit is administered in combination with one or more additional DNA transcription units, each comprising DNA encoding a different antigen of the immunodeficiency virus operatively linked to a promoter. As indicated by the Examiner, the Specification describes immunization with multiple DNA transcription units for HIV, an example of an immunodeficiency virus. The Specification describes a variety of transcription units appropriate for immunization in the case of HIV (see the Specification at page 45, line 16 and following (Example 11)). The Specification also describes immunization with multiple DNA transcription units for SIV, a second immunodeficiency virus (see Examples 13 and 14). Therefore, Claims 45-49 are enabled by the Specification.

These examples of immunizing with multiple transcription units in immunodeficiency viruses are representative of the types of multiple transcription units useful in the current invention. One of skill in the art, given the Specification, would recognize that several such transcription units could be used for immunization against immunodeficiency viruses, as described in the Specification. Furthermore, one of ordinary skill, given the Specification, would recognize that use of several transcription units would be particularly advantageous against influenza, as well as for HIV, given the number of strains of virus which cause each disease. Applicants have disclosed the best mode of the invention. They are not required to provide examples for every possible permutation of the invention.

<u>Rejection of Claims under 35 U.S.C. 112, second paragraph</u>

The Examiner rejected Claims 1, 16, 17, 32, 44 and 52, stating that "It is not clear from these claims whether or not the DNA transcription unit is expressed in the cells of the vertebrate." The Examiner further stated that "It is necessary to include this limitation in the claims otherwise it is not clear how the antigen would induce an immune response."

The claims have been amended to indicate that the DNA transcription unit is expressed in the cells of the vertebrate.

The Examiner also rejected Claim 4, indicating that the use of the word "capable" renders the claim vague and indefinite, in that "It is not clear whether or not a protective immune response is induced." Claim 4 has been cancelled, thereby rendering this rejection moot.

The Examiner also rejected Claim 53, indicating that the phrase "one or more" renders the claim vague and indefinite, in that "The composition of the vector is not clear from this description." The claim has ben amended to indicate that the DNA transcription unit is administered in combination with at least one additional DNA transcription unit comprising DNA encoding a different antigen of an influenza virus operatively linked to a promoter region.

Rejection of Claims under 35 U.S.C. 103

The Examiner set forth several rejections under 35 U.S.C. 103. The rejections are addressed below in the order in which they were raised in the Office Action.

A. Rejection of Claims As Unpatentable over Felgner (WO 90/11092) in view of Huylebroeck et al.

The Examiner rejected Claims 1-7, 10-14, 16-22, 24-26, 29-38, 41-49, and 51-56 as being unpatentable over Felgner (WO 90/11092) in view of Huylebroeck *et al*.

Teachings of the References Cited

1. Felgner

Felgner describes methods of delivering RNA or DNA polynucleotides into a vertebrate cell by interstitial delivery, exemplified by mRNA vaccination of mice to produce gp120 protein of the human immunodeficiency virus (HIV). Felgner states that an antibody response was elicited in the mice. Felgner does not describe any protective immune response.

2. Huylebroeck et al.

Huylebroeck *et al.* describe use of DNA in cell culture systems to produce the influenza virus protein hemagglutinin (HA). Huylebroeck *et al.* use recombinant, infectious, replication competent virus vector to express HA. The vector is an SV40 late replacement vector, which is designed to undergo episomal replication in eukaryotic cells. It includes the complete early region of the SV40 genome, as well as the SV40 origin of replication. The late region of the SV40 genome is replaced by a polylinker site that allows cloning of genes in the position for SV40 structural proteins. The expression of the SV40 early region plus the SV40 origin of replication supports episomal replication and amplification of the vector DNA in eukaryotic cells, to enhance levels of protein produced by the vector in the cell culture. The early region of the SV40 genome which supports episomal replication of DNA is the oncogenic region of SV40; the tumor antigens encoded by this region support transformation of cells and tumor induction.

The Huylebroeck *et al.* reference indicates that the constructs described may provide a basis for designing vaccines in which heterologous epitopes are incorporated into virus particles (discussion, p. 291). In contrast, the DNA constructs of the current invention are not

incorporated into self-replicating virus particles: they do not self-replicate. There is no teaching in Huylebroeck *et al.* that the virus particle constructs could be used *in vivo*. Furthermore, the constructs described by Huylebroeck *et al.* would be dangerous, if used *in vivo*, because they contain tumor-inducing genes. Such tumor inducing genes are inappropriate for introduction *in vivo*.

Improper Combination of the References

In order for references to be combined, there must be some teaching or suggestion in the prior art of record supporting the combination (ACS Hospital Systems, Inc. v. Montefiore Hospital, 221 USPQ 929, 933 (CAFC 1984)). However, no such teaching or suggestion appears in either Felgner or in Huylebroeck *et al.* Neither Felgner nor Huylebroeck *et al.* provides the necessary motivation to combine the references. One of ordinary skill in the art would not have been motivated to look beyond the general teachings of Felgner concerning delivery of polynucleotides, to the teachings of Huylebroeck *et al.* concerning influenza virus. There is no teaching or suggestion in Felgner that one of ordinary skill should look to the Huylebroeck *et al.* reference, which teaches influenza virus in particular, as opposed to looking to a reference describing any other possible viruses or pathogens. Furthermore, one of ordinary skill in the art would not have been motivated to look beyond the teachings of Huylebroeck *et al.* concerning influenza virus, to the teachings of Felgner concerning the delivery of polynucleotides. The methods of production of hemagglutinin described in Huylebroeck *et al.* differ in important aspects from the methods of generating desired antigens of the current invention. Huylebroeck *et al.* utilize cell culture systems to generate influenza hemagglutinin proteins. Huylebroeck *et al.* use an

infectious agent, replication competent vaccinia virus, to express hemagglutinin in an animal. In contrast, the current invention uses DNA encoding only the particular antigens, such as hemagglutinin. This DNA does not encode replication-competent virus, and is not capable of replication in the host. Huylebroeck *et al.* do not teach or suggest any other method of production of influenza hemagglutinin, such as production of influenza hemagglutinin in vivo through DNA inoculation, as in the current invention. Furthermore, the vectors employed by Huylebroeck *et al.* are inappropriate for use in humans, as they contain tumor inducing genes. One of ordinary skill in the art would not have been motivated by the teachings of Huylebroeck *et al.* to utilize solely the hemagglutinin DNA for vaccination, in order to generate antigen in the vaccinated organism.

Nonobviousness of the Claims in View of the Combination of References

Obviousness is established only if the teachings of the cited art would have suggested the claimed invention to one of ordinary skill in the art with a reasonable degree of certainty of successfully achieving the claimed results. One of ordinary skill in the art would not have been able to predict, given the teachings of Felgner and of Huylebroeck *et al.*, whether a protective response could have been achieved. Immune response such as that described in Felgner is not necessarily indicative of the ability of the vaccine to protect against infection. Furthermore, Felgner describes vaccination of mice with constructs that encode a protein from the human immunodeficiency virus (HIV), which is pathogenic to humans but not to mice. Therefore, it would not have been obvious to one of ordinary skill in the art that one could protect a vertebrate against any disease. Applicants have, for the

first time, demonstrated the protective effect of immunization with a DNA transcription unit. Thus, even if the references were improperly combined, the current invention would not have been rendered obvious, because one of ordinary skill in the art would not have had a reasonable expectation of success in achieving the claimed results.

B. Rejection of Claims As Unpatentable over Felgner in View of Tang

The Examiner rejected Claims 15 and 23 as being unpatentable over Felgner in view of Tang. The Examiner stated that:

> Felgner does not teach the use of a gene gun or microsphere encapsulation to deliver the DNA transcription unit. Tang teaches a method of immunizing with DNA by delivering DNA-coated gold microprojectiles directly into cells of a living animal. Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the methods described by Felgner with the delivery mechanism of Tang, due to the simplicity with which the DNA can be delivered to the animal, with the expectation of eliciting a more potent immune response demonstrated by the gene gun mechanism.

Applicants respectfully disagree with this assessment. Felgner is described above. Felgner does not teach or describe microprojectiles coated with DNA transcription units. Tang *et al.* describe immunization of mice with microprojectiles coated with plasmids containing human growth hormone (hGH) gene under the transcriptional control of either the human β-actin promoter or the cytomegalovirus (CMV) promoter. The mice produced antibody directed against hGH. Tang *et al.* do not describe protection against disease.

Claims 15 and 23 pertain to methods of immunizing a vertebrate against an infectious agent, comprising

administering to the vertebrate a DNA transcription unit which is microsphere-encapsulated; as a result, a humoral immune response, a cell-mediated immune response, or both, is elicited and the vertebrate is protected from disease caused by the infectious agent. These claims would not have been obvious to one of ordinary skill in the art, given the references. Neither Felgner nor Tang *et al.*, either alone or in combination, teaches or describes protective immunization using a DNA transcription unit. One of ordinary skill in the art, given the references, would not have had a reasonable expectation of succeeding in protecting a vertebrate against disease by immunizing the vertebrate with a microsphere-encapsulated DNA transcription unit.

C. Rejection of Claims As Unpatentable over Felgner in view of Both

The Examiner rejected Claims 8, 27 and 39 as being unpatentable over Felgner in view of Both. These claims were cancelled in the Preliminary Amendment filed in the U.S. Patent and Trademark Office on June 19, 1995. This rejection is therefore moot.

D. Rejection of Claims As Unpatentable over Felgner in view of Haynes

The Examiner rejected Claims 9, 28, 40 and 50 as being unpatentable over Felgner in view of Haynes (WO 93/17706). The Examiner stated that:

> Felgner does not teach an immune response against a simian immunodeficiency virus antigen. Haynes teaches a method of immunizing with a genetic construction encoding antigenic determinants of an immunodeficiency virus, specifically SIV and HIV (page 9, lines 28-29). Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the methods described by Felgner with the genes encoding the simian immunodeficiency virus

described by Haynes, recognizing the urgent need for a vaccine against immunodeficiency viruses.

Haynes describes vaccination against a virus, using a foreign genetic "construction" which includes "a promoter operative in cells of the animal and a protein coding region". The construction is coated onto carrier particles that are small in size in relation to the size of the animal cells. The carrier particles are then accelerated into the animal cells. Haynes describes preparation of the HIV constructions, and introduction of the constructions into cells in culture. Haynes describes delivery of the constructs into mice, and generation of antibodies. Haynes does not describe any simian immunodeficiency virus (SIV) constructs. Haynes does not teach or describe protection against disease.

The claims pertain to methods of immunizing a vertebrate against an infectious agent which is simian immunodeficiency virus, comprising administering to the vertebrate a DNA transcription unit; as a result, a humoral immune response, or cell-mediated immune response, or both, is elicited and the vertebrate is protected from disease caused by the immunodeficiency virus. The claimed invention would not have been obvious to one of ordinary skill in the art, given these references. First, one of ordinary skill in the art would not have been able to generate constructs for use in immunization against SIV, given these references, as neither reference, either alone or in combination, describes constructs for immunization against SIV. In contrast, Applicants have described generation of constructs for immunization against SIV.

Furthermore, neither Felgner nor Haynes, either alone or in combination, teaches protection against disease. Both Felgner and Haynes use a mouse model to generate antibodies to HIV. Because HIV is not pathogenic to mice,

one of ordinary skill in the art, given these references, would not have had a reasonable expectation of successfully protecting against disease. As discussed above and in the Declaration of Dr. Robinson, Applicants have investigated the use of the DNA constructs for SIV, in an appropriate monkey model, and have demonstrated that animals vaccinated by multiple routes remained free of symptoms of disease at one year after challenge.

Rejection under 35 U.S.C. 101

The Examiner provisionally rejected Claims 17-18, 21, 24-26 and 30-31 as claiming the same invention as that of Claims 11-14, 22-23 and 17-18 of copending application Serial No. 08/009,833. Applicants will address this rejection when claims are allowed in Serial No. 08/009,833.

Rejection of Claims Under the Judicially Created Doctrine of Obviousness-type Double Patenting

The Examiner provisionally rejected Claims 1-16, 19-20, 22-23, 27-29 and 32-56 as being unpatentable over Claims 1-2, 3, 7-14 and 17-24 of copending application Serial No. 08/009,833 in view of Ulmer *et al*. The Examiner stated that:

> Although the conflicting claims are not identical, they are not patentably distinct from each other because they differ only in scope from the prior application. The use of the claimed method for immunizing against other viral infections would be obvious to one of ordinary skill in the art. Also, the use of different routes of administration is well within the level of one skilled in the art.

The Examiner further stated that:

> Claims 3, 19 and 35 are obvious variations of the prior claims, in that retroviral promoter regions are well known in the art. The use of a retroviral promoter is documented in Ulmer *et al*.

> in which a rous sarcoma virus (RSV) promoter was used to immunize mice against influenza.

Applicants will address this rejection when claims are allowed in Serial No. 08/009,833. If appropriate, a Terminal Disclaimer will be filed.

Rejection under 35 U.S.C. 102(e)

The Examiner provisionally rejected Claims 17-18, 21, 24-26 and 30-31 as being anticipated by copending application Serial No. 08/009,833. Applicants will address this rejection when claims are allowed in Serial No. 08/009,833.

Rejection under 35 U.S.C. 103

The Examiner provisionally rejected Claims 1-16, 19-20, 22-23, 27-29 and 32-56 as being obvious over copending application Serial No. 08/009,833. The Examiner stated that:

> The use of the claimed method of 08/009,833 for immunizing against other viral infections and the use of a retroviral promoter would be obvious to one of ordinary skill in the art. Also, the use of different routes of administration is well within the level of one skilled in the art.

Applicants will address this rejection when claims are allowed in Serial No. 08/009,833.

Conclusion

In view of the amendments and the arguments presented above, Applicants respectfully request that the Examiner reconsider and withdraw all rejections.

If the Examiner believes that a telephone conversation will expedite prosecution of this application, the Examiner

is requested to call Applicants' Attorney at (617) 861-6240.

Respectfully submitted,

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